

**This Page Is Inserted by IFW Operations
and is not a part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- **BLACK BORDERS**
- **TEXT CUT OFF AT TOP, BOTTOM OR SIDES**
- **FADED TEXT**
- **ILLEGIBLE TEXT**
- **SKEWED/SLANTED IMAGES**
- **COLORED PHOTOS**
- **BLACK OR VERY BLACK AND WHITE DARK PHOTOS**
- **GRAY SCALE DOCUMENTS**

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

THIS PAGE BLANK (USPTO)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



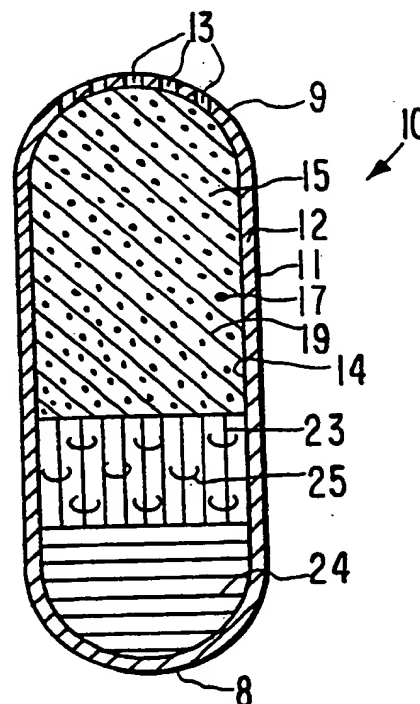
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) 2

(51) International Patent Classification n ⁵ : A61K 9/22, 31/71		A1	(11) International Publication Number: WO 91/01131
			(43) International Publication Date: 7 February 1991 (07.02.91)
(21) International Application Number: PCT/US90/03981		(74) Agent: SABATINE, Paul, L.; Alza Corporation, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).	
(22) International Filing Date: 16 July 1990 (16.07.90)			
(30) Priority data: 381,423 18 July 1989 (18.07.89) US		(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent).	
(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		Published <i>With international search report.</i>	
(72) Inventors: AYER, Atul, Devdatt ; 931 Bautista Court, Palo Alto, CA 94303 (US). BURKOTH, Terry, L. ; 711 Torrey Court, Palo Alto, CA 94303 (US). KUCZYNSKI, Anthony, L. ; 3875 Park Boulevard, #17, Palo Alto, CA 94306 (US). DETERS, Joseph, C. ; 979 Crooked Creek Drive, Los Altos, Ca 94022 (US).			

(54) Title: **DISPENSER COMPRISING IONOPHORE**

(57) Abstract

A dispenser is disclosed for delivering a beneficial ionophore to an animal. The dispenser comprises (1) a semipermeable housing defining an internal space, (2) at least one composition comprising an ionophore and a pharmaceutically acceptable carrier in the space, (3) an expandable hydrophilic composition in the space, (4) a dense member in the space, and (5) a passageway in the housing for delivering the ionophore from the dispenser.



DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Monaco
AU	Australia	FI	Finland	MG	Madagascar
BB	Barbados	FR	France	ML	Mali
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GR	Greece	NL	Netherlands
BJ	Benin	HU	Hungary	NO	Norway
BR	Brazil	IT	Italy	PL	Poland
CA	Canada	JP	Japan	RO	Romania
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
DE	Germany	LU	Luxembourg	TD	Chad
DK	Denmark			TG	Togo
				US	United States of America

DISPENSER COMPRISING IONOPHOREDESCRIPTION OF TECHNICAL FIELD

5 This invention pertains to a dispenser comprising an ionophore. More particularly, the invention concerns a dispenser for the controlled administration of an ionophore to an animal for treating an infectious disease, for improving feed efficiency, and for the enhancement of growth of the animal.

10

DESCRIPTION OF BACKGROUND OF
THE INVENTION

15 Ionophores, or ion-bearers, as reported in Ann. N.Y. Acad. Sci., Vol. 264, pp 373-86, (1975), are polyether antibiotics that modulate the physiological transport of ions across biological membranes, and alter the characteristics of fermentation in the animal resulting in favorable metabolic changes. These valuable properties of ionophores led to their use as feed additives by the
20 livestock industry. For example, the ionophores, when fed to ruminants, resulted in an improved feed-gain ratio, as reported in Feedstuffs, pp 14, 15 and 22, (1989). In one accepted use, ionophores are fed to feedlot cattle in confinement for improved feed efficiency. In this use the ionophore first is mixed with a finely
25 ground nonmedicated feedstuff to produce a premix, which premix is added to an air-dry feed for feeding to cattle, including steers and heifers.

30 While the above described prior art use of ionophores results in improved feed efficiency, usually of from 5 to 8 percent, or higher, for steers and heifers, as reported in Feedstuffs, supra, serious shortcomings accompany this use. For example, since the ionophore is mixed with feed, one shortcoming is the difficulty to ascertain the amount of ionophore ingested by the animal because of
35 feedlot losses such as spillage and scatter. Another shortcoming resides in the absence of controlled administration of known amounts

of the ionophore over time, as the composition of the feed charged with the ionophore can vary with feed millers. Also, ionophores are sensitive to moisture in the environment, which moisture can adversely affect their usefulness, and the handling and transport of feeds containing ionophores can result in the segregation of particles carrying ionophores and change the concentration level to which cattle are exposed when fed over time. Then, since ionophores usually are mixed with feeds daily, this requires extra labor that adds to the cost of the ionophore-feedstuff.

10

In the light of the above presentation, it will be appreciated by those versed in the dispensing art to which this invention pertains, that a pressing need exists for a dosage form that can deliver a valuable ionophore to a biological environment of use comprising livestock for both improved feed efficiency and the enhancement of growth of the livestock. The pressing need exists also for a dosage form that can store and deliver an ionophore at a controlled rate in a substantially constant dose per unit time over a prolonged period of time essentially independent of the environment of use, which environment of use pertains to livestock that are confined and to livestock in the pasture. It will be appreciated further by those versed in the dispensing art, that if such a novel and unique dosage form is provided that can administer an ionophore in a rate controlled dose over time and, simultaneously, provide the beneficial effects, the dosage form would represent an advancement and valuable contribution in the ionophore dosage form art.

15

20

25

OBJECTS OF THE INVENTION

30

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering an ionophore in a rate controlled amount, and which dosage form substantially overcomes the shortcomings associated with the prior art.

35

Another object of the present invention is to provide a dosage form for administering an ionophore in a rate controlled dose over a prolonged period of time to livestock for the improvement of feed efficiency and the enhancement of growth.

5

Another object of the present invention is to provide a dosage form for administering an ionophore in a lower overall dosage than the dose required if mixed with feedstuffs.

10

Another object of the present invention is to provide a dosage form comprising an ionophore antibiotic for administering it to a ruminant for producing metabolic changes in the rumen.

15

Another object of the present invention is to provide a dosage form comprising an ionophore that modulates the transport of ions across biological cellular membranes and when administered to ruminants the ionophores improve feed-gain ratios.

20

Another object of the invention is to provide a novel dosage form manufactured as an osmotic dispenser that can administer an ionophore to a biological receptor site to produce the desired beneficial ionophore effects.

25

Another object of the present invention is to provide a dosage form that can deliver a substantially water-insoluble ionophore at a controlled rate over time.

30

Another object of the present invention is to provide a dosage form for administering an ionophore, which dosage form comprises a composition that occupies space in the dosage form for displacing a composition comprising an ionophore from the dosage form.

35

Another object of the present invention is to provide a novel composition of matter comprising an ionophore, which composition can be dispensed from a dosage form to livestock in the pasture and to livestock in confinement.

Another object of the present invention is to provide a method for administering an ionophore in a rate-controlled dose per unit time for its beneficial effect.

- 5 Another object of the invention is to provide a dispenser with high drug loading of an ionophore that is self-contained, self-starting and self-powered in a fluid environment of use.

- 10 Another object of the invention is to provide a dispenser comprising a semipermeable wall that surrounds in at least a part an internal lumen, which lumen comprises a carrier comprising an ionophore and which carrier initially occupies a major portion of the lumen except for a driving member and a densifier, which dispenser delivers the ionophore by the combined physical-chemical operations
15 of the driving member urging the displaceable carrier through an opening in the wall to the environment of use.

- 20 Another object of the present invention is to provide a dispenser comprising a pharmaceutical carrier containing an ionophore that is a dispensable composition, that is innocuous, and when upon its displacement from the dispenser substantially avoids mammalian tissue irritation and interaction with mammalian protein tissue.

- 25 Another object of the invention is to provide a composition sized, shaped and adapted for housing in a dispenser which composition comprises from 0.01 weight percent (wt%) to 95 weight percent of an ionophore and a pharmaceutical carrier for the ionophore with the total amount of all ingredients in the composition equal to 100 weight percent.

30

Other objects, features and advantages of the invention will be more apparent to those versed in the dispensing and veterinary arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

35

BRIEF DISCLOSURE OF THE
INVENTION DRAWINGS

In the drawing figures, which are not drawn to scale, but are
5 set forth to illustrate various embodiments of the invention, the
drawing figures are as follows:

Figure 1 is a view of a dosage form designed and manufactured
as a dispenser for administering a beneficial ionophore to a warm-
10 blooded animal;

Figure 2 is a view of another dosage form provided by the
invention sized and adapted for administering a beneficial ionophore
to a warm-blooded animal over a prolonged period of time;
15

Figure 3 is an opened view of the dosage form of Figure 1
through 3-3 thereof for illustrating the structure of the dosage
form;

Figure 4 is an opened view of the dosage form of Figure 2
through 5-5 thereof for illustrating a different structural
embodiment of the dosage form;
20

Figure 5 is an opened view of the dosage form of Figure 1,
25 wherein the dosage form depicted in Figure 5 comprises a different
internal arrangement and exit means for delivering an ionophore from
the dosage form;

Figure 6 is an opened view of the dosage form of Figure 1,
30 wherein the dosage form in Figure 6 illustrates another embodiment of
the internal members and the exit means; and,

Figures 7 through 11 depict release rate patterns for
dispensers provided by the invention.

In the drawing figures and in the specification, like parts in related figures are identified by like reference numerals. The terms appearing earlier in the specification, and in the description of the drawing figures, as well as embodiments thereof, are further detailed
5 elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE
INVENTION DRAWINGS

10 Turning now to the drawings in detail, which drawings are examples of various dosage forms provided by the invention, and which examples are not to be construed as limiting, one example of a dosage form is seen in Figure 1. In Figure 1, a dosage form 10 is seen
15 comprising a body member 11 comprising a wall 12 that surrounds an internal lumen not seen in Figure 1. Dosage form 10 comprises a lead end 9 and a rear end 8. Lead end 9 comprises a wide exit passageway 13 for releasing a beneficial ionophore from dosage form 10 to a biological environment of use.

20 Figure 2 illustrates another embodiment of dosage form 10 provided by this invention. In Figure 2, dosage form 10 comprises lead end 9, rear end 8, body 11 and wall 12. Lead end 9 comprises more than one, or a multiplicity of exit passageways 13 through wall 12 for releasing a beneficial ionophore from dosage form 10.

25 In Figure 3, dosage form 10 of Figure 1, is seen in opened section through 3-3 of Figure 1. In Figure 3, dosage form 10 comprises lead end 9, rear end 8, a body 11, and a wall 12 that surrounds and forms an internal compartment 14 that communicates
30 through a wide exit passageway 13 with the exterior of dosage form 10. Wall 12, of dosage form 10, comprises totally a semipermeable composition, or wall 12 comprises at least in part a semipermeable composition. The remainder of wall 12, in the latter embodiment, may
35 comprise a composition that is substantially impermeable to the passage of an exterior fluid present in the environment of use, and it is substantially impermeable to the passage of ingredients present

inside dosage form 10. Both semipermeable or non-permeable portions of wall 12 are non-toxic and maintains its physical and chemical integrity during the delivery of the beneficial ionophore from dosage form 10.

5

Internal composition or lumen 14 comprises a first composition 15 and a second composition 16. The first composition 15 comprises a beneficial ionophore represented by dots 17, and the second composition 16 comprises a beneficial ionophore represented by dots 18. The first and second compositions comprise at least one or more than one ionophore. The first and second compositions comprise like or unlike ionophores. The first and second compositions comprise the same dosage unit amounts or the compositions comprise different dosage unit amounts of an ionophore. First composition 15 also comprises a pharmaceutically acceptable carrier represented by slanted lines 19 for ionophore 17, and the second composition 16 comprises a pharmaceutically acceptable carrier represented by slanted lines 20 for ionophore 18. Carriers 19 and 20 can be the same or different in compositions 15 and 16. In both embodiments, carriers 19 and 20 imbibe and/or absorb an external fluid that enters compartment 14 and form thereby a dispensable composition for transporting ionophores 17 and 18 from dosage form 10. First composition 15 and second composition 16 in a preferred optional embodiment comprise a binder, a tableting agent or a lubricant represented in composition 15 by wavy line 21 and in composition 16 by wavy line 22. Composition forming members 21 and 22 can be the same or they can be different in compositions 15 and 16.

Dosage form 10 in compartment 14 further comprises an expandable driving member 23 that is in contact with second composition 16. Expandable driving member 23 has a shape that corresponds to the internal shape of compartment 14. Expandable driving member 23, in the presence of an external fluid that enters compartment 14, imbibes and/or absorbs the fluid, increases in size, and thereby pushes against composition 16 to displace first composition 15 and second composition 16 from dosage form 10.

Compartment 14 also comprises a dense member 24 or densifier that is in contact with expandable member 23. Dense member 24 is an important component of dosage form 10 for keeping dosage form 10 in the rumen of an animal over a prolonged period of time.

5

Drawing Figure 4 depicts another manufacture provided by the invention. In drawing Figure 4, dosage form 10 comprises a body 11, and a wall 12 that surrounds and defines an internal compartment 14. Wall 12 comprises in a presently preferred embodiment a semipermeable composition that is substantially permeable to the passage of an external fluid, and it is substantially impermeable to the passage of ingredients contained in dosage form 10. Wall 12 is non-toxic and it keeps its physical and chemical integrity, that is, wall 12 doesn't erode during the dispensing period. Dosage form 10 also comprises a single composition 15. Composition 15 comprises at least one ionophore 17 homogeneously or heterogeneously dispensed in a pharmaceutically acceptable carrier 19. Carrier 19 is substantially dry during storage of dosage form 10, and when dosage form 10 is in operation in a fluid environment of use and carrier 19 is in contact with the fluid, carrier 19 changes from a rested state to a dispensable state form delivering ionophore 17 from dosage form 10. Dosage form 10 also comprises a dense member 24 positioned next to a wide-mouth passageway 13 in wall 12. Dense member 24 has a shape that corresponds to the shape of lead end 9 and to the inside shape of dosage form 10. A passageway 25 extends through dense member 20 for delivering beneficial composition 15 comprising ionophore 17 through dense member 24 and then through passageway 13 from dosage form 10. Compartment 14 also comprises an expandable member distant from passageway 13 at rear end 8. Expandable member 23 is in contact with composition 15 for displacing composition 15 through passageways 25 and 13 from dosage form 10. Composition 15 optionally comprises a binder, a tableting aid or a lubricant 22 for enhancing the manufacture and the displacement of composition 15 from dosage form 10.

35

Drawing Figure 5 depicts, in opened view, another manufacture provided by the invention. In drawing Figure 5, dosage form 10 comprises a body 11 and a wall 12 that surrounds and forms internal compartment 14. Internal compartment 14 comprises composition 15 which composition 15 comprises a pharmaceutically acceptable carrier 19 containing ionophore 17. Compartment 14 also comprises expandable member 23, which member 23 optionally comprises an osmotically effective solute 25. A densifier 24 is present in dosage form 10 position distant from lead end 9. Dosage form 10 comprises a multiplicity of passageways 13 in wall 12 at lead end 9. Passageways 13 comprise a number of smaller openings, generally in a shower-head or screen-like arrangement. The arrangement breaks-up composition 15 when emerging through opening 13.

Figure 6 illustrates another embodiment of dosage form 10 provided by the invention. In Figure 6, dosage form 10 is seen in opened section and it comprises rear end 8, leading end 9, body 11, openings 13, lumen 14, first composition 15, second composition 16, ionophore 17, ionophore 18, nontoxic carrier 19, nontoxic carrier 20, tableting aids 21, tableting aids 22, expandable member 23, densifier 24, and osmotically effective solute 25. Dosage form 10 comprises a multiplicity of exit openings 13 that are essentially means for breaking-up composition 15 and composition 16 as they are pushed at a controlled rate through the openings in wall 12. Exit means 13 also function to prevent a premature ejection of a composition from dosage form 10.

The dosage form of the invention can be sized and shaped for delivering an ionophore to a variety of animals. For example, the dosage form can be adapted for delivering an ionophore to ruminant animals including cattle, sheep, giraffe, deer, goat, bison and camels, and more particularly cattle and sheep, that comprise an important group of animals that require periodic administration of an ionophore. Dosage form 10 can embrace a capsule-like shape and in one design have a diameter of about 0.5 inches to 1 inch (1.3 cm to 2.5 cm) and a length of about 0.5 inches to 2.5 inches (1.3 cm to

6.6 cm). For use with cattle, dosage form 10 has a diameter of about 0.5 inches to 1.5 inches (1.3 cm to 3.8 cm), and a length of about 1 inch to 4 inches (2.5 cm to 10.2 cm).

5 While Figures 1 through 6 illustrate various dosage forms that can be made according to the invention, it is to be understood these dosage forms are not to be construed as limiting the invention as the dosage form can take other shapes, sizes and forms for delivering a beneficial ionophore to the biological environment of use. The
10 dosage form can be used in veterinary clinics, farms, zoos, laboratories, on the range, in feed lots, and other environments of use.

MODES OF PROVIDING THE INVENTION

15

In accordance with the practice of this invention it has now been found that wall 12 can be made with a wall forming composition that does not adversely affect the animal, and it does not adversely affect the beneficial ionophore and other ingredients in dosage form
20 10. Wall 12 is permeable, that is, the wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of ionophore. Typical materials used for forming wall 12 are, in one embodiment, cellulose esters, cellulose ethers, and cellulose ester-ethers. The cellulose
25 polymers have a degree of substitution, D.S., on their anhydroglucose unit of from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group.
30 Representative materials include a member selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate; cellulose acetate, cellulose diacetate, cellulose triacetate; mono-, di-, and tricellulose alkanylates; mono-, di-, and tricellulose aroylates, and the like. Exemplary polymers include
35 cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having a D.S. of 1.8 to 2.3 and an acetyl

content of 32% to 39%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of 21% to 35%; cellulose triacetate having a D.S. of 2 to 3 and an acetyl content of 34% to 44.8%, and the like. More specific cellulose polymers include cellulose propionate having
5 a D.S. of 1.8, a propyl content of 39.2% to 45% and a hydroxyl content of 2.8% to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13% to 15% and a butyryl content of 34% to 39%; cellulose acetate butyrate having an acetyl content of 2% to 29%, a butyryl content of 17% to 53% and a hydroxyl content of 0.5%
10 to 4.7%; cellulose triacylate having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate and cellulose trioctanoate; cellulose diacylate having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate;
15 coesters of cellulose such as cellulose acetate butyrate, cellulose acetate propionate, and the like.

Additional polymers include ethyl cellulose of various degrees of etherification with ethoxy content of from 40% to 55%; cellulose
20 acetate ethyl carbamate; cellulose acetate methyl carbamate; cellulose acetate diethyl aminoacetate; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586;
25 3,541,005; 3,541,006; 3,546,142; 4,595,583; 4,783,337; and the like. Semipermeable polymers also are disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132. Semipermeable lightly cross-linked polymers, semipermeable cross-linked poly(sodium styrene sulfonate), semipermeable cross-linked poly(vinylbenzyltrimethyl) ammonium
30 chloride; semipermeable polymers exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm²/hr . atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across a semipermeable membrane are disclosed in U.S. Pat. No. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers by Scott, J.R. and Roff
35 W.J., (1971) published by CRC Press Cleveland, OH.

Semipermeable wall 12 also can comprise a flux regulating agent. The flux regulating agent is a compound that assists in regulating the permeability of a fluid through the semipermeable wall. Flux regulating agents that increase the permeability of a wall to fluid, such as water, are essentially hydrophilic. The amount of regulator in the wall, when incorporated therein, generally is from about 0.01 weight percent, (wt%), to 35 wt%, or more. The flux regulator agents in one embodiment comprise a member selected from the group consisting of a polyhydric alcohol, polyalkylene glycol, polyalkylenediol, polyester of alkylene glycol, and the like. Typical flux enhancers comprise polyethylene glycol 300, 400, 600, 1500, 4000, 6000 and the like; low molecular weight glycols such as polypropylene glycol, polybutylene glycol, and polyamyleneglycol; the polyalkylenediols such as poly(1,3-propanediol), poly(1,4-butanediol), poly(1,6-hexanediol) and the like; aliphatic diols such as 1,3-butylene glycol, 1,4-pentamethylene glycol, 1,4-hexamethylene glycol, and the like; alkylene triols such as glycerine, 1,2,3-butanetriol, 1,2,4-hexanetriol, 1,3,6-hexanetriol, and the like; esters such as ethylene glycol dipropionate, ethylene glycol butyrate, butylene glycol dipropionate; and the like.

Semipermeable wall 12 optionally comprises a plasticizer, for imparting flexibility and elongation properties to the wall, for making the wall less brittle, and for enhancing the manufacturing properties of the wall. Plasticizers useful for the present purpose comprise dihexyl phthalate, butyl octyl phthalate, triacetin, dioctyl azelate, epoxidized tallate, sucrose acetate isobutyrate, epoxidized soybean oil, phosphate esters, tricresyl phosphate, triacetyl phosphate, adipate esters, sebacate esters, and other nontoxic plasticizers. The amount of plasticizer in wall 12 when incorporated therein, is about 0.01 wt% to 40 wt%, or more.

Representative of beneficial ionophores that can be dispensed using the dosage form of this invention comprise natural and synthetic ionophores. The ionophores are polyethers and they possess the ability to transport mono and divalent cations across lipid

bilayers, which lie within biological membranes. The ionophores possess unique properties which derive from their ability to perturb transmembrane ion gradients and electrical potentials. The ability of ionophores to complex and transport ions leads to their applications as antibiotics against gram-positive microorganisms, against mycobacteria, as growth promotants in ruminants such as cattle and sheep, and for improved feed utilization as seen by increasing the efficiency of meat production. Ionophores that can be stored and dispensed by the dosage form of this invention comprise a member selected from the group consisting of azolomycin, valinomycin, enniactin, monactin, nonactin, dinactin, trinactin, virginamycin, tetronasin, semduramicin, monensin, monensin sodium, monensin factor B, monensin factor C, nigericin, narasin also known as methyl salinomycin, salinomycin, isolasalocid, lasalocid, lysocellin, septamycin, laidomycin, lonomycin, lenotemycin, grisorixin, ferensimycin, alborixin, rosgamicin, ethermoycin, sodium lysocellin, and the like. The ionophores also comprise the pharmaceutically acceptable derivatives having ionophore activities, such as the pharmaceutically acceptable salts, the alkylated and alkenyl derivatives, the monoglycoside and diglycoside derivatives, the hydroxylated derivatives, the free acid, the hydrate, and the like. In one presently preferred embodiment, the ionophores exhibit a molecular weight of about 350 to 2500. The presently preferred amount of an ionophore in a dosage form, present in a single composition, or in a first and second composition, generally is from 10 milligrams to 100 grams. The amount of ionophore in a first composition can be from 10 mg to 100 g and the amount of ionophore in a second composition can be from 10 mg to 100 g with the total amount of ionophore in both compositions equal to 100 g. The amount of ionophore in a first and in a second composition can be the same or different. The compositions can comprise one, or more than one like or unlike ionophore. The dosage form provided by the invention can deliver various dosage amounts of an ionophore, for example, from 10 mg per day to 500 mg per day for 200 days or longer. The ionophores are known in the ionophore art in Kirk-Othmer Encyclopedia, Vol. 3, pp 47-64, (1978); Ann. N.Y. Acad. Sci., Vol. 264, pp 373-86, (1975);

and ACS Sym., Ser. 140, pp 1-22, (1980). The ionophore can be present as a base, as a salt, or as a derivative thereof.

The pharmaceutically acceptable carrier 19 and 20 forming the first and second compositions 15 and 16 and comprising ionophores 17 and 18 comprise pharmaceutically acceptable polymers that are hydrophilic, nontoxic, and substantially free of reaction with an ionophore and other members forming dosage form 10. The pharmaceutically acceptable carrier comprising an ionophore provides unexpected advantages comprising (a) the ability to store a high dosage amount up to 95 wt% of an ionophore, (b) the ability to dispense an ionophore in controlled, small doses over a prolonged time up to 6 months, (c) the ability to substantially protect a fluid sensitive ionophore from fluid that enters the dosage form by harboring the ionophore within its polymeric structure; and (d) the ability to charge high loadings of an ionophore in a polymer carrier that undergoes change from a rested state to a dispensable state possessing a dispensable viscosity, or to a semisolid dispensable state during operation of the dosage form. The polymer carriers useful for the present purpose comprise a member selected from the group consisting of polyethylene oxide polymers having a 200,000 to 7,500,000 molecular weight; carboxy vinyl polymers, sometimes referred to as carboxypolymethylene, commercially available as Carbopol® polymer possessing a 200,000 to 5,000,000 molecular weight; poly(vinyl pyrrolidone) having a 125,000 to 460,000 molecular weight; poly(hydroxyalkyl methacrylate) having a 100,000 to 5,000,000 molecular weight; polysaccharides such as agar, karaya, tragacanth, algin, guar, nanthan, and the like, having a 50,000 to 2,000,000 molecular weight and the like.

30

Expandable layer 23 useful for displacing the first and/or the second composition from the dosage form comprises a hydrogel composition. The hydrogel composition is noncross-linked or optionally lightly cross-linked and it possesses osmotic properties like the ability to imbibe an exterior fluid through the semipermeable wall and exhibit an osmotic pressure gradient across

35

the semipermeable wall. The polymer exhibits the ability to retain a significant fraction of the imbibed fluid in the polymer structure. The polymers in a preferred embodiment are gel polymers that can swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase, thereby pushing and displacing the composition comprising the ionophore from the dosage form. The swellable, hydrophilic polymers also are known as osmopolymers. The polymers can be of plant, animal or synthetic origin. Polymeric materials useful for forming the expandable layer comprise anionic and cationic hydrogels; polyelectrolyte complexes; a mixture of agar and carboxymethyl cellulose; a composition comprising methyl cellulose mixed with sparingly cross-linked agar; water swellable polymer of N-vinyl lactams; polyethylene oxide possessing a 1,000,000 to 10,000,000 molecular weight; starch graft polymers; sodium carboxymethylcellulose having a 90,000 to 1,000,000 molecular weight; a composition comprising sodium carboxymethylcellulose and a member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and the like. Representative polymers possessing hydrophilic properties are known in U.S. Pat. Nos. 3,865,108; 4,002,173; 4,207,893; and 4,327,725; and in Handbook of Common Polymers by Scott and Roff, published by the Cleveland Rubber Company, Cleveland, OH.

Expandable polymer layer 23 optionally comprises an osmotically effective compound. Osmotically effective compounds also are known as osmotically effective solutes and as osmagents. The osmotically effective compounds exhibit an osmotic pressure gradient across semipermeable wall 12, and they imbibe fluid into compartment 14. The presence of this imbibed fluid provides added fluid for the expandable polymer to absorb and increase its volume, and the imbibed fluid continuously fills the driving area of the compartment and forms a push member that urges the first and/or second compositions from dosage form 10. Osmotically effective compounds useful for the present purpose comprise magnesium sulfate, magnesium chloride, sodium chloride, potassium chloride, lithium chloride, potassium sulfate, sodium sulfate, mannitol, urea, sorbitol, inositol, sucrose,

glucose, a mixture of sodium chloride and magnesium chloride, a mixture of potassium chloride and sucrose, and the like. The osmotic pressure in atmospheres, atm, of osmotically effective compounds suitable for the invention will be greater than zero atm, generally
5 from eight atm up to 500 atm, or higher. The amount of osmotically effective compound blended homogeneously or heterogeneously with the swellable polymer is from 0.02 wt% to 50 wt%. Osmotically effective polymers are known in U.S. Pat. Nos. 4,595,583 and in 4,783,337.

10 Composition forming members, or tableting aids 21 and 22 used to provide compositions 15 and 16 comprise binders that impart cohesive qualities to the composition such as poly(vinyl pyrrolidone), natural and synthetic gums such as sodium alginate methylcellulose, hydroxypropylmethylcellulose, Veegum®, waxes, and
15 the like; lubricants for enhancing the rate of flow of the tablet granulation, to prevent adhesion to dies and punches during tableting processes such as a magnesium stearate, calcium stearate, stearic acid, talc, lycopodium, and the like; coloring agents for esthetic qualities and identification such as FD&C Blue No. 1; surfactants
20 that aid in dispensing the ionophore after its release from the dosage form, such as anionic, cationic, nonionic and amphoteric surfactants; and the like. Composition members are disclosed in Pharmaceutical Sciences, Remington, 14th Ed., (1970). The amount of composition member present in the composition is about 0.01 wt% to
25 20 wt%.

The dense member 24, also referred to as densifier 24, is used in delivery system 10 to retain the dosage form in the rumen-reticular sac of a ruminant. Dense member 24 lets dosage form 10
30 remain in the rumen over a prolonged period of time, rather than letting it pass into the alimentary tract and be eliminated therefrom. As dosage form 10 remains in the rumen, beneficial ionophore is delivered at a controlled rate to the ruminant over a prolonged period up to 6 months or longer. Generally, dense member
35 24 will have a density of from about 1.0 to 8, or higher, with the density in a presently preferred embodiment exhibiting a specific

17.

gravity of from 1.5 to 7.6. For the ruminants cattle and sheep, it is presently preferred dense member 24 exhibit a density to assure complete system density of 2 to 3, or greater. Materials that have a density that can be used for forming dense member 24 include iron, iron shot, iron shot coated with iron oxide, iron shot magnesium alloy, steel, stainless steel, copper oxide, a mixture of copper oxide and iron powder, and the like. Dense member 24 in dosage form 10 can embrace different embodiments. For example, dense member 24 can be machined, or cast as a single, solid piece made of stainless steel having a density of 7.6. The solid member is made having a curved shape that corresponds to the internal shape of system 10. Dense member 24 in another manufacture can be a solid member having an axially aligned bore that extends through the length of the member. In another embodiment dense member 20 can comprise a plurality of dense pellets.

The expression, "passageway 13", as used herein, denotes an opening or a means in wall 12 suitable for releasing the composition comprising the ionophore from dosage form 10. The invention provides a passageway for releasing a composition intact, and it provides a passageway member for dividing the original composition into smaller compositions as it is released from dosage form 10. The release of a composition from dosage form 10, in either instance, embodies a combination of osmotic hydrodynamic pumping and diffusion properties through an exit passageway or through a series of exit passageways functioning as an exit port. The dosage form provided by this invention maximizes the release by osmotic pumping and minimizes the release by diffusion, thereby substantially avoiding mechanical agitation dependent drug release. The release rate pattern from a drug dosage form, for example, designed to deliver 85 mg/day of the drug lysocellin is as follows in Equation (1):

$$\left[\frac{dm}{dt} \right]_t = \left[\frac{dm}{dt} \right]_o + \left[\frac{dm}{dt} \right]_d \quad (1)$$

wherein;

5 $\left[\frac{dm}{dt} \right]_t$ is the total amount of drug released from the device per unit time (mg/day);

10 $\left[\frac{dm}{dt} \right]_o$ is the amount of drug released per unit time (mg/day) due to osmotic pumping; and

15 $\left[\frac{dm}{dt} \right]_d$ is the amount of drug released per unit time (mg/day) due to diffusion.

Then, assuming that negligible water migrates into the drug composition through the wall, Equation (2) follows:

20
$$\left[\frac{dm}{dt} \right]_o = V \cdot \rho_d \cdot L = \left[\frac{k}{h} \right] A_p \cdot \Delta\pi \cdot \rho_d \cdot L \quad (2)$$

wherein;

25 V is the release rate from the dosage form at 40°C in cc/day;

30 ρ_d is the drug + pharmaceutical carrier density in mg/cc;

L is the percent drug loading;

35 k is the water permeability of the wall at 40°C in $\frac{\text{cm}^3 \text{ mil}}{\text{cm}^2 \text{ hr atm}}$;

h is the wall thickness in mil (or in mm);

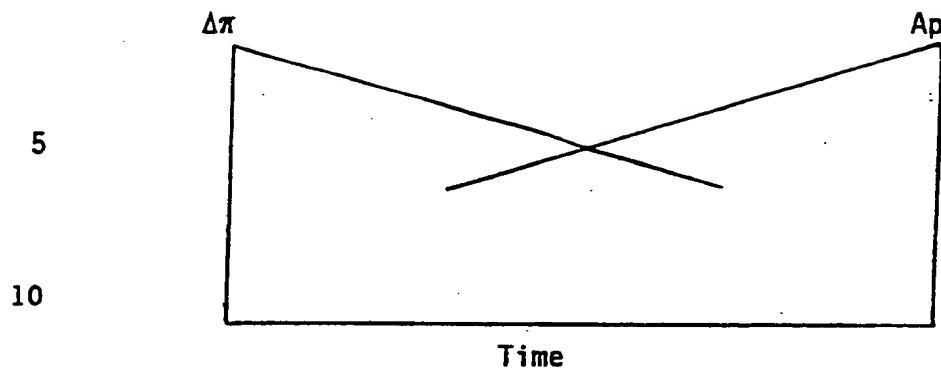
40 A_p is the surface of the push-composition in contact with the wall. The bottom and top surfaces of the push composition are in contact with density element and the drug composition respectively; and,

45 $\Delta\pi$ is the water imbibition pressure atm.

During operation of the dosage form, $A_p \times \Delta\pi$ remains constant; and their operation can be illustrated by the accompanying graph wherein $A_p \times \Delta\pi = C$; and,

50

19



15 wherein any decrease in osmotic activity is compensated for by an increase in the area of the push composition in contact with the wall. Therefore, it follows according to Equations (3) and (4):

$$20 \quad \left[\frac{dm}{dt} \right]_o = \left[\frac{k}{h} \right] C \cdot \rho_d \cdot L \quad (3)$$

$$25 \quad \left[\frac{dm}{dt} \right]_o = \left[\frac{k\pi \times Ap}{h} \right] \rho_d \cdot L \quad (4)$$

The amount of drug delivered due to diffusion into an environment of use initially free of drug is set forth by Equation 5:

$$30 \quad \left[\frac{dm}{dt} \right]_d = \left[\frac{D \text{ Sep } Cs}{h} \right] L \quad (5)$$

35 wherein:

40 $\left[\frac{dm}{dt} \right]_d$ is the amount of formulation, comprising lysocellin and pharmaceutical carrier diffusing through the exit port per unit time (mg/day);

D is the diffusion coefficient of the formulated drug in ruminal fluid in cm^2/day ;

45 Sep is the surface area of the exit port in cm^2 ;

h is the thicknesses of the diffusion layer in cm;

50 Cs is the solubility of formulated drug in ruminal fluid in mg/ml;

L is the percent drug present in the formulation; and,
 $D/h = K$ is the dissolution rate constant in cm/day.

5 The composition comprising the ionophore drug is intermittently eroded at the exit passageway in the rumen, and the thickness of the diffusion layer varies from zero to several mm in thickness. The diffusion layer at the dosage form environment of use interface is very thin and will have minimal effect on the amount of formulated
 10 drug diffusing through the exit passageway into the ruminal fluid. The two major factors which contribute to the diffusion through the exit passageway are:

- (1) Surface area of the exit port (Sep); and,
- (2) Solubility of the pharmaceutical carrier and the
 15 lysocellin ionophore in ruminal fluid (Cs).

Following the above presentation, the osmotic release rate for the dosage form comprising a lysocellin ionophore composition can be calculated to be 67 mg/day. The total release rate $(dm/dt)_t$ for the
 20 lysocellin is 85 mg/day. The diffusional release rate for lysocellin is therefore 18 mg/day.

The effect of the exit passageway diameter increase on the lysocellin release rate was calculated to give the following values
 25 (for the 85% drug loading):

$(dm/dt)_t$	$(dm/dt)_o$	$(dm/dt)_d$	Exit passageway diameter	Sep exit passageway surface area
mg/day	mg/day	mg/day	mils	cm ²
68.7	66.7	2.04	100	0.051
74.8	66.7	8.13	200	0.203
85.0	66.7	18.31	300	0.456
85.0	66.7	18.31	100 X 9	0.456
99.2	66.7	32.52	400	0.810

The diffusional release increases with an increase in the exit diameter. For the 300 mil exit diameter the diffusional release is 21.5%, but for a 400 ml exit the diffusional release is 33% of the total lysocellin release rate.

5

Accompanying Figure 7 shows the effects of the exit passageway diameter on the diffusional release of lysocellin. In Figure 7, one mil equals 0.0254 mm.

10

Accompanying Figure 8 shows the effects of the exit passageway diameter on the total release of lysocellin from the dosage form.

Accompanying Figure 9 depicts the functionality of the dosage form. The release rate $(dm/dt)_t$ from the dosage form is about 85 mg/day in vivo. In Figure 9, the in vivo testing in the rumen of a cow is indicated by squares, the in vitro testing in buffer at pH 8 is indicated by diamonds, and the in vitro testing in artificial ruminal fluid is indicated by triangles. The buffer was a pH 8 buffer consisting of 140.70 g of potassium phosphate, and 38.64 g of sodium hydroxide dissolved in 20 liters of distilled water. The artificial rumen fluid consists of 124.69 g of sodium acetate, 53.99 g of sodium propionate, 21.00 g of sodium bicarbonate, 81.02 g of sodium succinate, and 29.92 g of butyric acid dissolved in 20 liters of distilled water then bubbled with carbon dioxide for 10 minutes.

25

Accompanying Figure 10 shows the results of the effect of the exit diameter increase on the lysocellin release rate. In Figure 10, the horizontal line connected by dots indicates a constant release rate of 80 mg/day. The line with squares depicts the release rate through a 400 ml passageway for a composition comprising lysocellin and a hydrophilic polymer having a 7,500,000 molecular weight; the line with triangles pointed up depicts the release rate through a 300 mil passageway by a composition comprising lysocellin and a hydrophilic polymer having a 7,500,000 molecular weight; the line with the triangles pointed down depicts the release rate through a 300 mil passageway for a composition comprising lysocellin and a

35

hydrophilic polymer having a 5,000,000 molecular weight; and, the line with squares depicts the release rate through a 200 mil orifice for a composition comprising a 200 mil passageway and a hydrophilic polymer having a 5,000,000 molecular weight; and the line in dashes across the figure indicates a release of 80 mg/day.

The table presented immediately below sets forth the results obtained by comparing the calculated values with the experimental values obtained for a 79% lysocellin loading in a drug composition.

10

15

20

25

Drug Carrier	Calculated (dm/dt) _t	Experimental (dm/dt) _t	Exit Port Diameter
Hydrophilic Polymer	mg/day	mg/day	mils
5,000,000 Molecular Weight	79 69	77 *60	300 200
7,500,000 Molecular Weight	92 79	90 *66	400 300

The data with an asterisk indicates the experimental value was prepared as follows: The dosage form was designed with one drug composition, comprising 79% or 6 g of lysocellin, and one expandable composition and one composition comprising calcium carbonate. The composition comprising calcium carbonate was used as a filler layer to conserve ionophore. The expandable composition was placed between the ionophore composition and the calcium carbonate composition. The ionophore composition faced the exit port and the calcium carbonate composition faced the density element. Within about three weeks after the experiment began the expandable composition began to occupy space between the wall and the calcium carbonate composition, thereby diverted some of the push energy away from the exit port, resulting in the indicated values.

DESCRIPTION OF EXAMPLES OF
THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be construed as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become more apparent to those skilled in the dispensing art in light of the present disclosure, the drawings and the accompanying claims.

10

EXAMPLE 1

A dosage form manufactured in the shape of a dispenser for the controlled delivery of lysocellin is made as follows: first, 85 g of lysocellin is passed through a 40 mesh screen. Then, 14.75 g of polyethylene oxide having a 5,000,000 molecular weight is passed through a 40 mesh screen. The just prepared lysocellin and polyethylene oxide are mixed thoroughly with 0.75 g of hydroxypropylmethyl cellulose having a 11,000 molecular weight to provide a homogeneous mix. Then, 30 ml of denatured, anhydrous ethanol is slowly added to the blending mixture, and all the ingredients mixed for an additional 2 to 3 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen to provide a drug composition.

Then, the drug composition is divided into two portions and compressed to make two different shaped tablets, or drug compositions. For one drug tablet, 7.06 g of the drug composition is compressed with a hydraulic press using a flat bottom tablet punch, and a deep-concave, top tablet punch. The other tablet is made by compressing 7.06 g of the drug composition using a flat bottom and flat top tablet punch.

Next, an expandable composition is prepared by passing separately through a 40 mesh screen the following ingredients: 84.7 g of sodium carboxymethylcellulose with a 700,000 molecular weight, 9.4 g of hydroxypropylcellulose with a 60,000 molecular weight, 4.7 g of sodium chloride and 1.0 g of ferric oxide. All of the above ingredients are thoroughly mixed to provide a homogeneous mass. Then, with continuous mixing, 40 ml of denatured alcohol is added slowly and the mixing continued for 2 to 3 minutes. The wet granulation is passed through a 20 mesh screen, dried at room temperature for 16 hours and again passed through a 20 mesh screen. Finally, 0.2 g of magnesium stearate is added to the granulation and the ingredients mixed in a rollermill for 3 to 4 minutes. The expandable composition is made into a tablet by compressing 5.2 g of the composition in a hydraulic press using a flat top and flat bottom tablet punch.

Next, a wall forming member designed and shaped like a cup is prepared as follows: first, 76 g of cellulose acetate butyrate having a butyryl content of 37% and 13% acetyl content, 15 g of polyethylene glycol having a 400 molecular weight and 9 g of triethyl citrate are mixed into a homogeneous mass. Then, 10.5 g of the mixture is injection molded to make a semipermeable walled cup with an average wall thickness of 65 mils.

The dispenser is assembled as follows: first, a 300 mil exit port is drilled through the concave end of the semipermeable cup. The first described drug tablet is then inserted into the semipermeable cup so that its convex top fits into the concave end of the cup. Then, the second described drug tablet is inserted into the cup so that it is flush against the flat end of the first inserted drug tablet. Next, the expandable tablet is inserted so that it is flush against the second drug tablet. Then, a 64 g iron densifier is inserted into the cup so that its flat end is against the expandable tablet. Finally, the wall is sealed as the open end is heated, pressed against the densifier and cooled to room temperature.

Dispensers prepared according to this example were placed into the fistulated cow's rumen. The dispensers were removed from the rumen at different time intervals to measure the amount of lysocellin released per unit time. Accompanying Figure 11 illustrates the controlled and continuous release of lysocellin at a rate of 85 mg/day for 126 days. In the figure, the squares denote the cumulative amount of lysocellin released (grms.) at different time (days) intervals, and the number of dispensers in the study where seven.

EXAMPLE 2

A dispenser sized and adapted for the controlled delivery of lysocellin is made according to the procedure set forth in Example 1, with all conditions as previously described, except that in this example the drug composition comprising the lysocellin is present as a single composition. The single composition weighs 14.12 g and comprises the polyethylene oxide having a 5,000,000 molecular weight, a hydroxypropylmethylcellulose having a 11,200 molecular weight, and the lysocellin ionophore.

EXAMPLE 3

A dispenser for administering two different carboxylic ionophores, monensin and lasalocid, for increasing feed efficiency in ruminants is manufactured according to the procedure of Example 1. In this example, the dispenser comprises two ionophore compositions, with each composition comprising a different ionophore. A first composition nearest the exit port comprises monensin sodium, polyethylene oxide having a 5,000,000 molecular weight and hydroxypropylmethylcellulose having a 11,200 molecular weight. The second composition is in immediate contact with the first composition. The second composition comprises lasalocid, polyethylene oxide having a 3,000,000 molecular weight and hydroxypropylmethylcellulose having a 22,000 molecular weight. The rest of the dispenser is as described in Example 1. The use of two

different ionophores delivered into the rumen operates to maintain maximum feed efficiency. The dispenser can be manufactured for administering the first ionophore composition for 50 to 60 days followed by delivering the second composition for 50 to 60 days.

5

EXAMPLE 4

A dispenser for administering two ionophores, narasin and tetronasin, simultaneously is manufactured as follows: first, 40 g of narasin and 40 g of tetronasin are blended into a homogeneous mass. Then, 14.75 g of a carboxyvinyl polymer of acrylic acid lightly cross-linked with polyallyl ether of sucrose and having a 3,000,000 molecular weight is mixed with the ionophores and the mixture passed through a 40 mesh stainless screen. Then, the freshly prepared mix is thoroughly blended with 1.25 g of hydroxypropylmethylcellulose possessing a 22,000 molecular weight and the blend screened as described. Next, all the screened ingredients are added to the bowl of a commercial blender and the ingredients dry blended for 15 to 20 minutes to produce a homogeneous blend. Then, a granulation fluid is prepared comprising 20 ml of ethanol and 20 ml of isopropyl alcohol and the granulating fluid added to the blending bowl as follows: first 10 ml is sprayed into the bowl with constant blending, then 30 ml of the granulation fluid is added slowly to the bowl and the wet mass blended for another 15 to 20 minutes. Then, the wet granules are passed through a 16 mesh screen and dried at room temperature for 24 hours. Then, 2 g of magnesium stearate is added to the dry granules, and the ingredients roll-mixed for 10 to 15 minutes on a standard two-roll mill.

Next, an expandable composition is prepared as follows: 85 g of polyethylene oxide having a 5,000,000 molecular weight is screened through a 40 mesh screen, then, 36 g of sodium chloride is passed through a 40 mesh screen and the ingredients added to a mixing bowl and blended for 10 to 15 minutes. Then, a granulation fluid is prepared by mixing 175 ml of methanol and 75 ml of isopropyl alcohol, and the granulation fluid added to the blending bowl in two steps.

First, 75 ml of the granulation fluid is sprayed into the bowl with constant blending, then 175 ml of the granulation fluid is added slowly to the bowl and the wet blend mixed for 15 to 20 minutes to produce a homogeneous mass. Then, the wet blend is passed through a
5 16 mesh screen, spread on a stainless steel tray and dried at room temperature at 22.5°C for 16 hours. The dried blend is passed through a 16 mesh screen, then roll milled with 3 g of stearic acid on a two-roll mill for 20 to 30 minutes.

10 Next, a number of laminated drug cores are prepared by pressing the two compositions on a Stokes® layer press. The composition containing the ionophore is fed into the cavity of the press and compressed into a solid layer. Then, the composition comprising the expandable hydrophilic hydrogel and osmotic solute is fed into the
15 cavity overlaying the compressed layer and pressed into a solid layer to form a two-layered ionophore expandable core.

Next, the core is placed in contacting arrangement with a density member inside an elongated mold. The expandable layer is in
20 contact with the density member. The density member comprises frangible stainless steel having a density of 7.5 g/cc. The mold has an inside circumference slightly larger than the circumference of the core density member arrangement. The space between the inside of the mold and the arrangement is filled with a semipermeable composition.
25 On drying the semipermeable composition forms a thin semipermeable wall around the laminated arrangement. The wall coated laminated member is removed from the mold and further coated with a semipermeable composition.

30 The semipermeable wall forming composition comprises 90 g of cellulose acetate butyrate having an butyryl content of 38%, and 10 g of poly(ethylene glycol) 4000 in a solvent comprising 2000 ml of methylene chloride and 700 ml of methanol. The laminated arrangement are coated with the semipermeable wall forming composition until the
35 desired wall surrounds the laminated arrangement. The coated laminated arrangement are then spread on a tray and the solvent

evaporated in a circulating air oven at 40°C. After cooling to room temperature a full mouth passageway is cut through the semipermeable wall connecting the composition comprising the ionophores with the exterior of the dispenser. The dispenser will deliver the ionophores over a 130 day period of time.

EXAMPLE 5

A dispenser for delivering an ionophore to livestock is made by following the above examples. The dispenser of this example is 75 mm long and 25 mm in diameter. The dispenser comprises a pair of compositions in contacting arrangement, with each composition comprising 6,000 mg of an ionophore selected from the group consisting of lasolocid, lysocellin, septamycin, nigericin, dianemycin, monensin and salinomycin, 1,054 mg of polyethylene oxide possessing a 5,000,000 molecular weight, 162.50 mg of hydroxypropylmethylcellulose possessing a 11,200 molecular weight, and 125 mg of magnesium stearate. The dispenser comprises a single expandable layer in contact with the pair of ionophore composition. The expandable composition comprises 4,405 mg of sodium carboxymethyl cellulose having a 700,000 molecular weight, 490 mg of hydroxypropylcellulose, 245 mg of sodium chloride, 50 mg of ferric oxide, and 15 mg of magnesium stearate. The device contained a 64,000 mg iron densifier, a 10,500 mg cellulosic rate controlling wall, and a 400 mil diameter exit orifice.

EXAMPLE 6

A dispensing device for the controlled delivery of an ionophore into the digestive tract of an animal is manufactured as follows: first, 57 g of cellulose acetate having an acetyl content of 39.8% and 1.3 kg of cellulose acetate butyrate having a butyryl content of 38% are sized and then combined with 2.2 g of Citroflex® -2 triethylcitrate and 0.3 kg of polyethylene glycol 400 in the bowl of a large Hobart® mixer. After mixing for 20 minutes, the blended material is transferred to the feed hopper of a Van Dorn injection

molder, which is equipped with a suitable mold to produce a 7.5 g cellulose cup having the approximate dimensions 6.3 cm in height x 2.1 cm in width and a wall thickness of 0.13 cm.

5 Next, 4.0 g of a hydrophilic expandable member comprising 70:30 ratio of sodium carboxymethylcellulose to sodium chloride, lubricated with 1% magnesium stearate is compressed using 10,000 lbs. of force in a Carver® laboratory press equipped with a tablet tool and then inserted into the cup.

10

 Next, an ionophore composition comprising 10 g of an ionophore selected from the group consisting of lonomycin, lenotemycin, etheromycin, isolasalocid, laidomycin sodium salt, semduramicin, and alborixin potassium salt, 2.1 g of poly(ethylene oxide) having a
15 3,500,000 molecular weight, 0.325 g of hydroxypropylmethylcellulose having a 11,200 molecular weight and 0.5 g of magnesium stearate pressed into a solid table is inserted into the cup against the expandable member.

20 Then, an iron density element comprising four 50 mm exit passageways, that possess the dual function of aiding in the retention of the dispenser in the rumen of an animal, and serving as a flow moderator through its multiplicity of passageways is inserted into the open end of the dispenser and seated against the ionophore
25 composition. The protruding lip of the cup is heated until softened using a hot air gun capable of delivering 600°F air, and the lip crimped over the perimeter of the density element to provide the dispenser.

30

METHOD OF USING THE INVENTION

 An embodiment of the invention pertains to a method for administering a beneficial ionophore at a controlled rate to the
35 rumen of a ruminant. In carrying out the method, a dispenser is placed into a balling gun provided with an ejecting means, the gun

inserted into the mouth of the animal beyond the base of the tongue, and the dispenser gently ejected by applying pressure to an ejection plunger in the gun, thereby sending the dispenser into the rumen. More specifically the method comprises the steps of: (A) admitting
5 into an animal's rumen a dispenser comprising : (1) a wall comprising in at least a part a semipermeable polymer composition permeable to the passage of fluid and substantially impermeable to the passage of an ionophore, the wall surrounding; (2) an internal lumen comprising a layer comprising a beneficial ionophore and a pharmaceutically
10 acceptable carrier for the ionophore; (3) a layer of an expandable hydrophilic polymeric composition in the lumen; (4) a dense member in the lumen for maintaining the dispenser in the rumen over a prolonged period of time, and at least one exit passageway in the wall that communicates with the composition comprising the ionophore and the
15 carrier; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall, which fluid contacts the composition comprising the ionophore and forms a dispensable composition, and contacts the expandable composition causing the expandable
20 compositions to expand and push against the ionophore composition; and (C) delivering the beneficial ionophore composition from the lumen by the expandable composition continually expanding against the ionophore composition causing the ionophore to be dispensed in a
beneficially effective amount through the passageway at a controlled
25 rate to the rumen over a prolonged period of time.

Inasmuch as the foregoing specification comprises presently preferred embodiments of the invention, it is to be understood that various improvements and modifications may be made herein in
30 accordance with the inventive principles disclosed, without departing from the scope of the invention.

The claims:

1. A dispenser for delivering a beneficial ionophore to a fluid environment of use, the dispenser comprising:
 - (a) a wall comprising in at least a part a
5 semipermeable composition permeable to the passage of fluid, which wall surrounds;
 - (b) a lumen;
 - (c) a composition comprising from 10 mg to 100 g of an ionophore and a pharmaceutically acceptable carrier for the ionophore
10 in the lumen;
 - (d) a hydrophilic polymeric composition in the lumen that expands in the presence of fluid for pushing the composition comprising the ionophore from the dispenser;
 - (e) a densifier in the lumen, said densifier having a
15 specific gravity greater than the specific gravity of fluid present in the environment of use; and,
 - (f) a passageway in the wall for delivering from 15 mg a day to 350 mg a day of the ionophore from the dispenser.
- 20 2. The dispenser for delivering the beneficial ionophore to a fluid environment of use according to claim 1, wherein the ionophore is lysocellin.
- 25 3. The dispenser for delivering the beneficial ionophore to a fluid environment of use according to claim 1, wherein the ionophore is a member selected from the group consisting of lonomycin, lenotemycin, etheromycin, isolasalocid, laidomycin, semduramicin, and alborixin.
- 30 4. The dispenser for delivering the beneficial ionophore to a fluid environment of use according to claim 1, wherein the ionophore is a member selected from the group consisting of lasalocid, septamycin, nigericin, dianemycin, monensin, and salinomycin.

5. The dispenser for delivering the beneficial ionophore to a fluid environment of use according to claim 1, where the dispenser delivers the ionophore for 180 days.

5 6. A dispenser for delivering a beneficial ionophore to a fluid environment of use, wherein the dispenser comprises:

(a) a wall comprising in at least a part a nontoxic composition permeable to the passage of fluid, the wall surrounding and forming;

10 (b) a compartment;

(c) a first composition in the compartment comprising a beneficial ionophore and a pharmaceutically acceptable carrier for the ionophore;

15 (d) a second composition in the compartment comprising a beneficial ionophore and a pharmaceutically acceptable carrier for the ionophore;

(e) a third composition in the compartment comprising an osmotic composition that expands when contacted by fluid and displaces the first and second compositions from the dispenser:

20 (f) a densifier in the compartment, said densifier having a specific gravity greater than the specific gravity of fluid present in the environment of use; and,

(g) a passageway in the wall for delivering the first and second compositions from the dispenser over a period of time.

25

7. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the first composition is lysocellin.

30 8. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the second composition is lysocellin.

35 9. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the first composition and the second composition comprise the same ionophore.

10. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the first composition and the second composition comprise different ionophores.

5 11. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the dispenser delivers an ionophore for 200 days.

10 12. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the first composition comprises an ionophore selected from the group consisting of valinomycin, enniactin, monactin, nonactin, dinactin, trinactin, virginamycin, tetronasin, semduramicin, monensin, monensin sodium, nigericin, narasin, and salinomycin.

15 13. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the first composition comprises an ionophore selected from the group consisting of isolasalocid, lasalocid, lysocellin, septamycin, 20 laidomycin, lonomycin, lenotomycin, grisorixin, alborixin, ethermycin, azolomycin, and sodium lysocellin.

25 14. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the second composition comprises a member selected from the group consisting of valinomycin, enniactin, monactin, nonactin, dinactin, trinactin, virginamycin, tetronasin, semduramicin, monensin, monensin sodium, nigericin, narasin and salinomycin.

30 15. The dispenser for delivering a beneficial ionophore to a fluid environment of use according to claim 6, wherein the ionophore in the first composition comprises an ionophore selected from the group consisting of isolasalocid, lasalocid, lysocellin, septamycin, laidomycin, lonomycin, lenotomycin, grisorixin, alborixin, 35 ethermycin, azolomycin, and sodium lysocellin.

16. A composition for dispensing from a drug delivery dispenser to livestock over a prolonged period of time, said composition comprising 10 mg to 100 g of an ionophore selected from the group consisting of valinomycin, enniactin, monactin, nonactin, 5 dinactin, trinactin, virginamycin, tetronasin, semdur-amicin, monensin, monensin sodium, nigericin, narasin, and salinomycin, and a pharmaceutically acceptable poly(ethylene oxide) carrier comprising a 200,000 to 7,500,000 molecular weight.
- 10 17. A composition for dispensing from a drug delivery dispenser to livestock over a prolonged period of time, said composition comprising 10 mg to 100 g of an ionophore selected from the group consisting of isolasalocid, lasalocid, lysocellin, septamycin, laidomycin, lonomycin, lenotomycin, grisorixin, 15 alborixin, ethermoycin, azolomycin and sodium lysocellin, and a pharmaceutically acceptable poly(ethylene oxide) carrier comprising a 200,000 to 7,500,000 molecular weight.
- 20 18. A laminate useful for manufacturing a delivery system for delivering a beneficial ionophore to a ruminant, wherein the laminate comprises: a first lamina comprising an ionophore selected from the group consisting of valinomycin, enniactin, monactin, nonactin, dinactin, trinactin, virginamycin, tetronasin, sem-duramicin, monensin, monensin sodium, nigericin, narasin, salinomycin, 25 isolasolocid, lasolocid, lysocellin, septamycin, laidomycin, lonomycin, lenotomycin, grisorixin, alborixin, ethermoycin, azolomycin and sodium lysocellin; which first lamina is in laminar arrangement with a second lamina, said second lamina comprising at least one of the ionophore present in the first lamina.
- 30 19. A method for administering to an animal a biologically active ionophore, said method comprising:
- (a) admitting orally into the animal a dispenser comprising:

(1) a wall that surrounds and forms an internal lumen, the wall comprising a composition permeable to the passage of fluid and substantially impermeable to the passage of an ionophore;

5 (2) a composition in the lumen comprising a biologically active ionophore selected from the group consisting of valinomycin, enniactin, monactin, nonactin, dinactin, trinactin, virginamycin, tetronasin, semduramicin, monensin, monensin sodium, nigericin, narasin, salinomycin, isolasalocid, lasalocid, lysocellin,
10 septamycin, laidomycin, lonomycin, lenotomycin, grisorixin, alborixin, ethermoycin, azolomycin and sodium lysocellin, and a pharmaceutically acceptable carrier for the ionophore said carrier comprising a poly(ethylene oxide) comprising up to 90 wt% of the ionophore;

15

(3) a hydrophilic composition in the lumen that expands when contacted by fluid thereby exerting pressure against the ionophore composition for displacement in from the lumen;

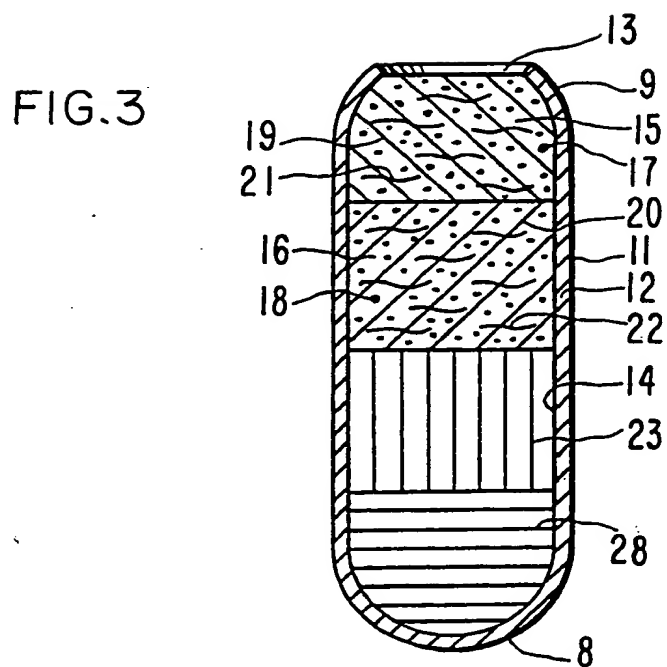
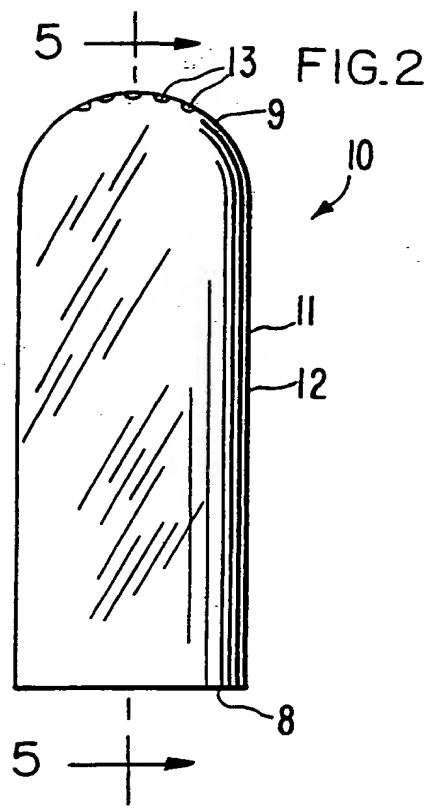
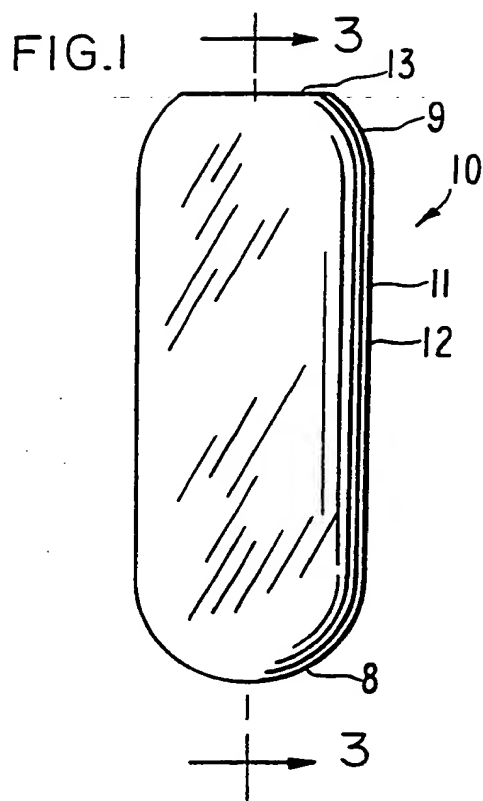
20

(4) a densifier in the lumen for maintaining the dispenser in the animal over time, said densifier having a density greater than the density of the fluid present in the animal; and

(5) a passageway in the dispenser for delivering
25 the biologically active ionophore from the dispenser; and,

(b) administering the biologically active ionophore by the ionophore composition absorbing fluid to form a dispensable composition and by the hydrophilic composition absorbing fluid,
30 expanding and displacing the ionophore composition through the passageway to the animal at a controlled rate over time.

1 / 5



2/5

FIG. 4

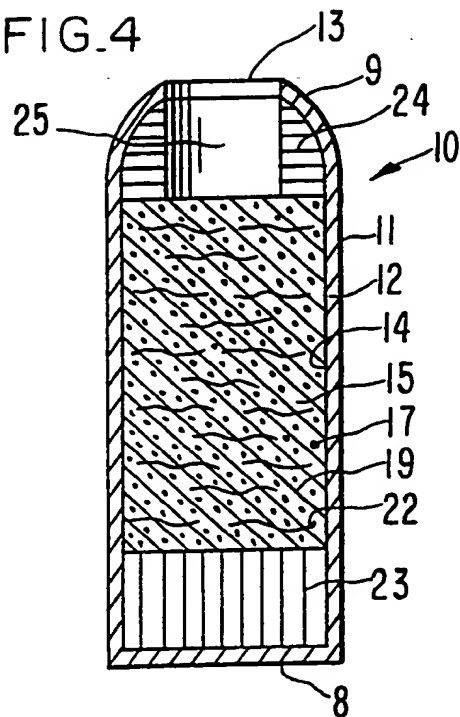


FIG. 5

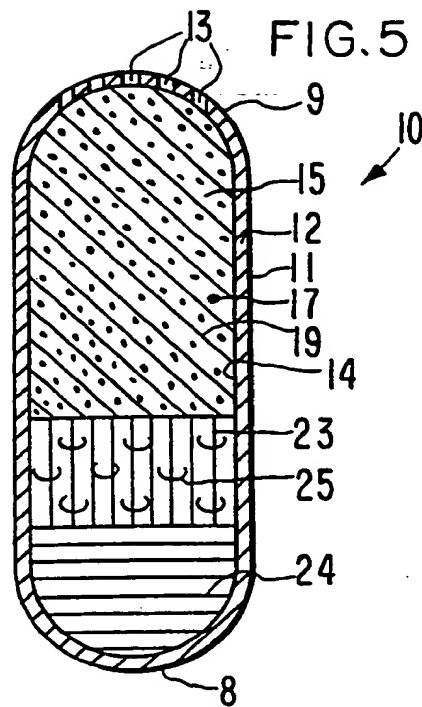
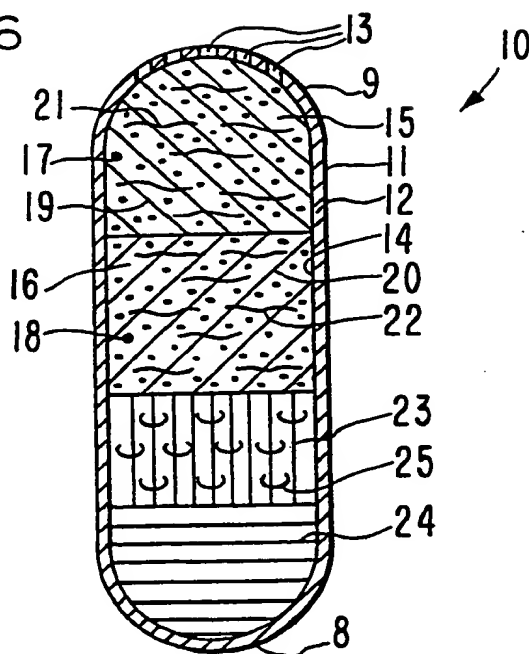


FIG. 6



3/5

FIG. 7

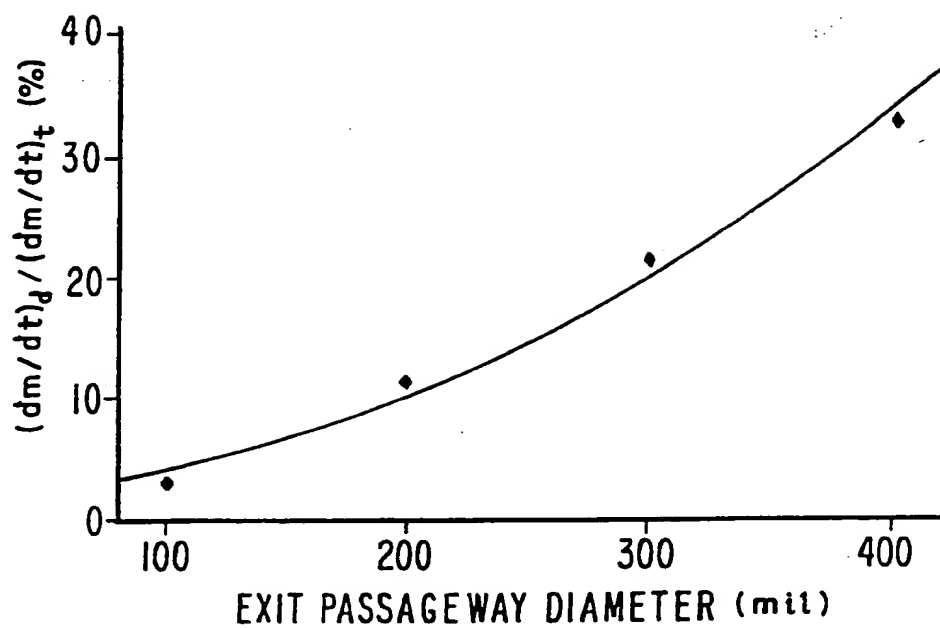
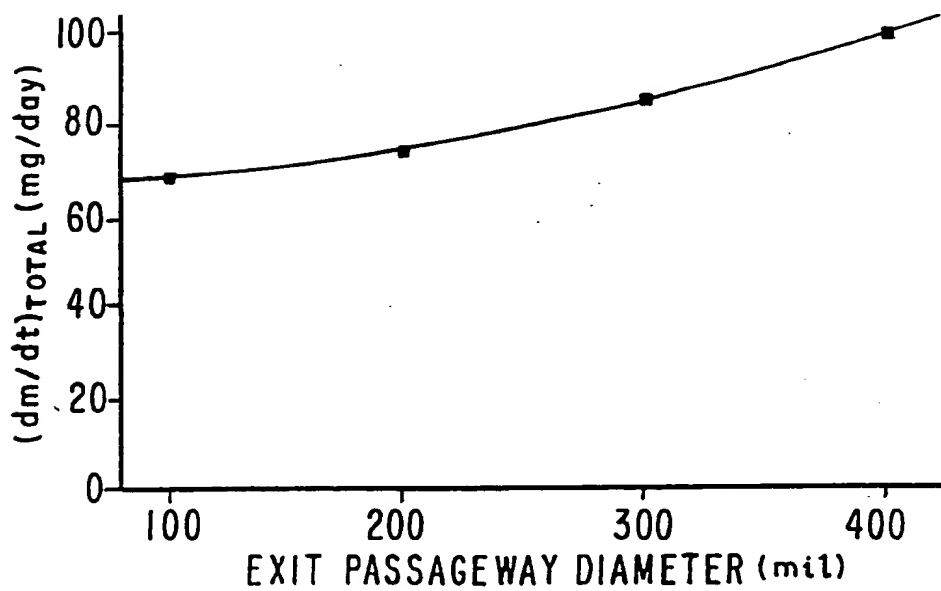


FIG. 8



4/5

FIG. 9

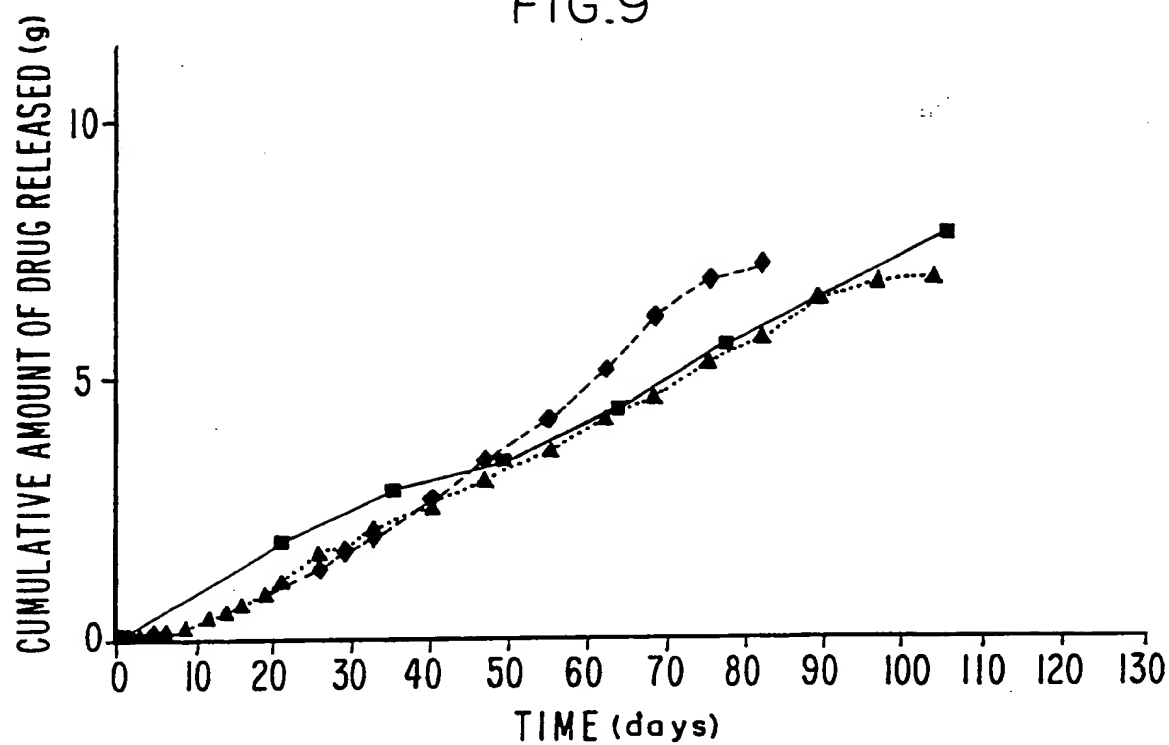
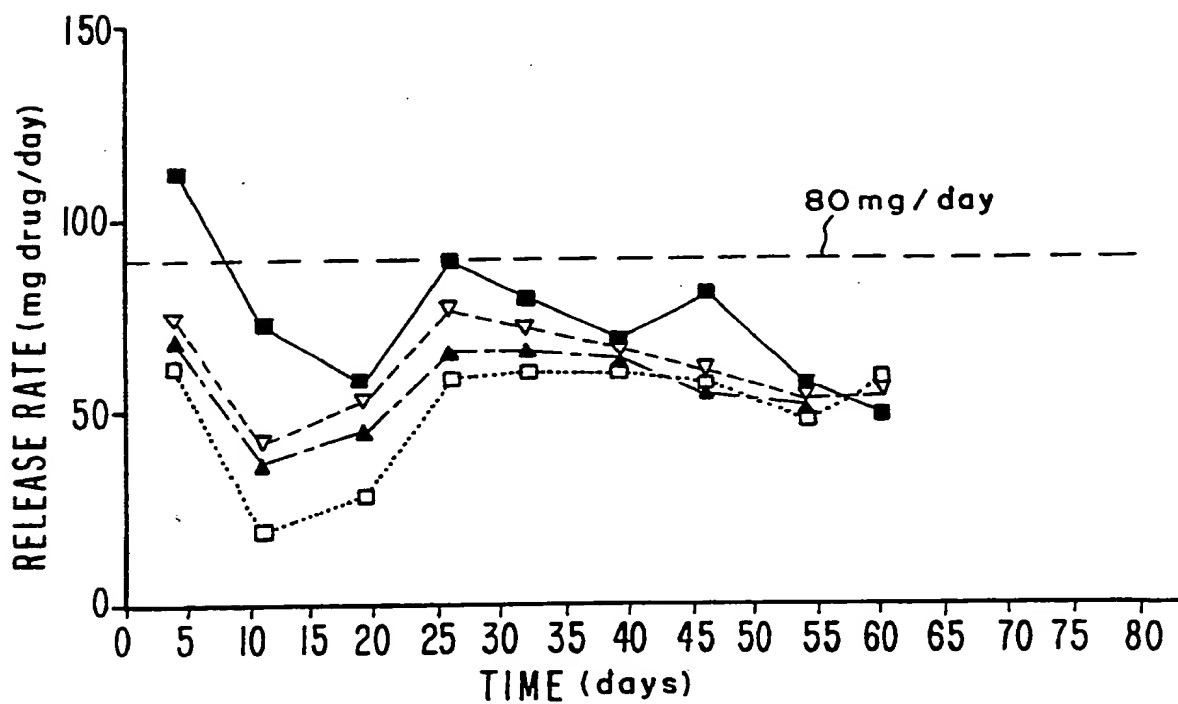
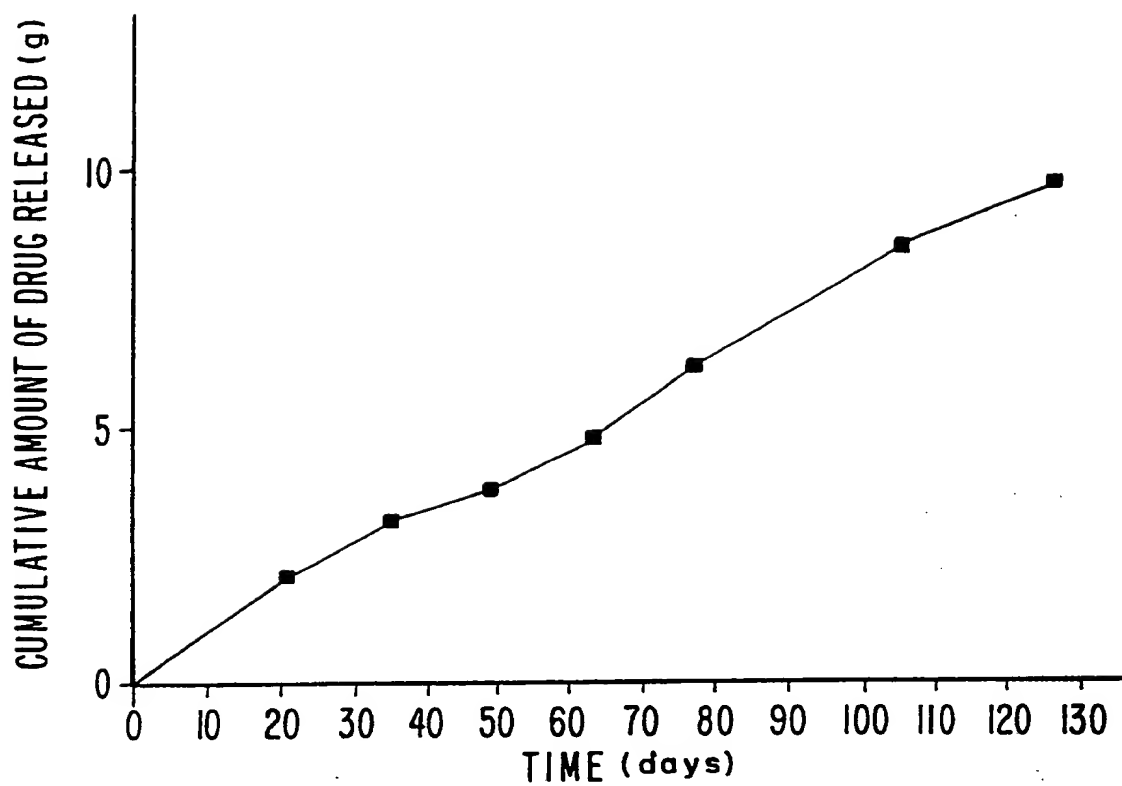


FIG. 10



5/5

FIG. II



INTERNATIONAL SEARCH REPORT

PCT/US 90/03981

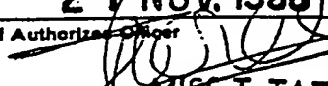
International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : A 61 K 9/22, A 61 K 31/71					
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none;">Classification System </td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">IPC⁵</td> <td style="border: none; vertical-align: top;">A 61 K</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div>		Classification System	Classification Symbols	IPC ⁵	A 61 K
Classification System	Classification Symbols				
IPC ⁵	A 61 K				

III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	GB A, 2179252 (ALZA CORP.) 4 March 1987 see the whole document, in particular page 7, line 30 <div style="text-align: center;">---</div>	1-19
Y	EP, A, 0164241 (ELI LILLY & CO.) 11 December 1985 see page 4, lines 5-18; pages 41-49, examples 1-6; claim 10 <div style="text-align: center;">---</div>	1-19
Y	EP, A, 0025699 (ELI LILLY & CO.) 25 March 1981 see page 3, lines 17-25; page 11, line 23 - page 13, line 31; pages 26-27, examples 8-10 <div style="text-align: center;">---</div>	1-19
Y	WO, A, 82/00094 (COMMONWEALTH SCIENTIFIC & INDUSTRIAL RESEARCH ORGANIZATION) 21 January 1982 see pages 11,12, example 2 <div style="text-align: center;">-----</div>	1-19

- Special categories of cited documents: ¹⁴
- "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

IV. CERTIFICATE	
Date of the Actual Completion of the International Search <div style="text-align: center; font-size: large;">7th November 1990</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-size: x-large;">21 NOV. 1990</div>
International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center;">  H. S. T. A. F. A. R. </div>

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9003981

SA 39216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/11/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2179252	04-03-87	AU-B- 578374	20-10-88
		AU-A- 6102086	19-02-87
		BE-A- 905283	01-12-86
		DE-A- 3626559	09-04-87
		FR-A- 2586189	20-02-87
		JP-A- 62044249	26-02-87
		NL-A- 8602015	16-03-87
		US-A- 4865598	12-09-89
EP-A- 0164241	11-12-85	US-A- 4649042	10-03-87
		AU-B- 580782	02-02-89
		AU-A- 4308285	05-12-85
		JP-A- 61002850	08-01-86
		SU-A- 1484280	30-05-89
EP-A- 0025699	25-03-81	AT-B- 366911	25-05-82
		AU-B- 539868	18-10-84
		AU-A- 6216480	19-03-81
		BE-A- 885180	11-03-81
		CA-A- 1129737	17-08-82
		CH-A- 641665	15-03-84
		FR-A, B 2464701	20-03-81
		GB-A, B 2059767	29-04-81
		JP-A, B, C 56045654	25-04-81
WO-A- 8200094	21-01-82	CA-A- 1177397	06-11-84
		EP-A, B 0056379	28-07-82
		US-A- 4671789	09-06-87